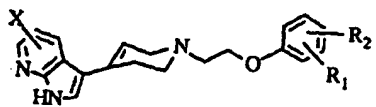




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<p>(21) International Application Number: PCT/US00/10628 (22) International Filing Date: 20 April 2000 (20.04.00) (30) Priority Data: 09/296,736 22 April 1999 (22.04.99) US (71) Applicant: AMERICAN HOME PRODUCTS CORPORATION [US/US]; Five Giralda Farms, Madison, NJ 07940-0874 (US). (72) Inventors: MEWSHAW, Richard, Eric; 251 West DeKalb Pike, Apartment B-509, King of Prussia, PA 19406 (US). MEAGHER, Kristin, Lynne; 400 Dutch Neck Road, Apartment L-8, Highstown, NJ 08520 (US). (74) Agents: NAGY, Michael, R.; American Home Products Corporation, Patent Law Dept. - 2B, One Campus Drive, Parsippany, NJ 07054 (US) et al.</p>		<p>(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: AZAINDOLE DERIVATIVES FOR THE TREATMENT OF DEPRESSION</p> <div style="text-align: center;">  <p>(1)</p> </div> <p>(57) Abstract</p> <p>Compounds useful in the treatment of diseases affected by disorders of the serotonin-affected neurological systems, such as depression and anxiety, are provided having formula (I) wherein: R₁ and R₂ form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy; or pharmaceutically acceptable salts thereof.</p>		

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AZAINDOLE DERIVATIVES FOR THE TREATMENT OF DEPRESSION

FIELD OF INVENTION

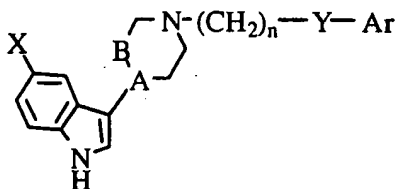
This invention relates to compounds useful for the treatment of diseases
5 affected by disorders of the serotonin-affected neurological systems, such as
depression and anxiety. More specifically, the present invention is directed to aryl
piperazinyl cyclohexyl derivatives useful for the treatment of such disorders.

BACKGROUND OF INVENTION

10 Pharmaceuticals which enhance the neurotransmission of serotonin (5-HT) are
useful for the treatment of many psychiatric disorders, including depression and
anxiety. The first generation of non-selective serotonin-affecting drugs operated
through a variety of physiological means which caused them to possess numerous
undesired side-effects. The more recently prescribed drugs, the selective serotonin
15 reuptake inhibitors (SSRIs), act predominately by inhibiting 5-HT, which is released
at the synapses, from being actively removed from the synaptic cleft via a presynaptic
serotonin transport carrier. Since SSRIs require several weeks before they exert their
full therapeutic effect, this 5-HT blockade mechanism cannot fully account for their
therapeutic activity. It is speculated that this two week induction which occurs before
20 a full antidepressant effect is observed, is due to the involvement of the 5-HT_{1A}
autoreceptors which suppress the firing activity of 5-HT neurons, causing a
dampening of the therapeutic effect. Studies suggest that after several weeks of SSRI
administration, a desensitization of the 5-HT autoreceptors occurs allowing a full
antidepressant effect in most patients. (See, e.g., Le Poul et al., Arch. Pharmacol.,
25 352:141 (1995)). Hence, it is believed that overriding this negative feedback by using
5HT_{1A} antagonists would potentially increase and accelerate the clinical
antidepressant response. Recent studies by Artigas et al., Trends Neurosci., 19:378-
383 (1996), suggest a combination of 5-HT_{1A} activity and inhibition of 5-HT uptake
within a single molecular entity can achieve a more robust and fast-acting
30 antidepressant effect.

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European Patent Application No. 0714894A1 discloses the preparation of the following compounds as 5HT1A agonists for the treatment of migraine headaches.



5

wherein:

A-B is -CH-CH₂ or -C=CH-;

X is H, halo, C₁-C₄ alkoxy, C₁-C₄ alkylthio, C₁-C₄ alkyl, benzyloxy, hydroxy or carboxamido;

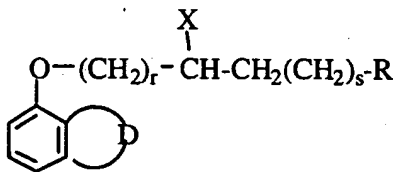
10 Y is O, S or a bond;

n is 1-4; and

Ar is 1-naphthyl, 2-naphthyl, phenyl or phenyl, mono-substituted with a substituent selected from the group consisting of halo, C₁₋₄ alkoxy, C₁₋₄ alkylthio, C₁₋₄ benzyloxy hydroxy or trifluoromethyl.

15

U.S. Patent No. 5,627,196 discloses compounds of the following formula as having effects on serotonin-related systems.



20

wherein r is 0-4;

s is 0-1; and

D is a residue which combines with the carbon atoms to which it is attached to complete a pyrrolyl, imidazolyl, pyridinyl, pyrazinyl, pyridazinyl or pyrimidinyl

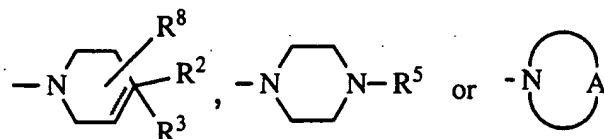
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group;

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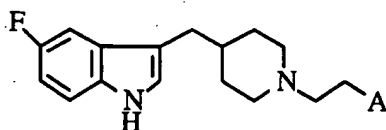
X is hydrogen, phenyl, hydroxy or methoxy provided that X is hydrogen or phenyl
where r is 0; and

R is -NH-R₁,



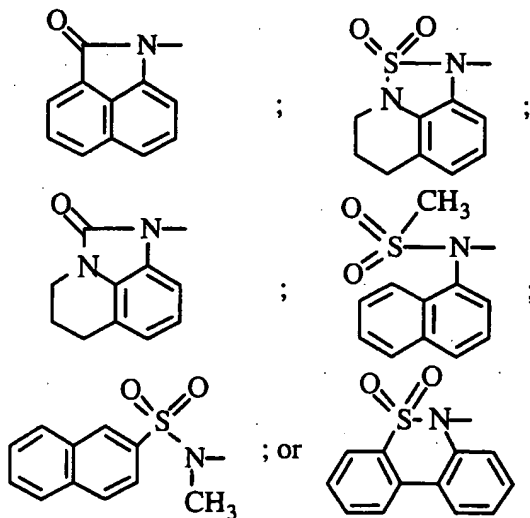
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Malleron et al., J. Med. Chem. 36:1194-1202 (1983) discloses indole derivatives as serotonin uptake inhibitors having the basic formula:



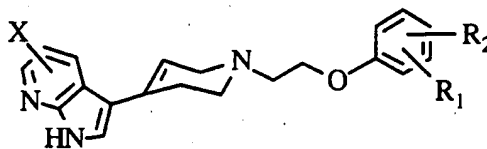
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wherein A may be:



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Thus, according to the present invention there are provided compounds of Formula I:



I

5 wherein:

R_1 and R_2 form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and

X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;

or pharmaceutically acceptable salts thereof.

10

Preferred compounds of the present invention are preferably those of Formula I, wherein:

R_1 and R_2 form a carbocyclic or heterocyclic ring of 5-6 atoms; and X is hydrogen;

or pharmaceutically acceptable salts thereof.

15

Most preferably, the compounds of the present invention are selected from the following:

3-{1-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine;

20 3-{1-[2-(1H-Indol-4-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine; and

5-{2-[4-(1H-Pyrrolo[2,3-b]pyridine-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethoxy}-quinoline.

25

As used herein, the term "alkoxy" is meant to include both straight and branched carbon chains containing 1-6 carbon atoms. The term "halogen" is meant to include fluorine, chlorine, bromine and iodine. The term "heterocyclic ring" mean saturated or unsaturated rings containing one or more heteroatoms, preferably

- 5 -

selected from oxygen, nitrogen and sulfur. Preferred examples contain, 5 or 6 atoms, particular examples, are 1,4-dioxane, pyrrole and pyridine. The term "carbocyclic ring" means saturated or unsaturated carbon rings such as aryl or cycloalkyl, preferably containing 5 or 6 carbon atoms..

5

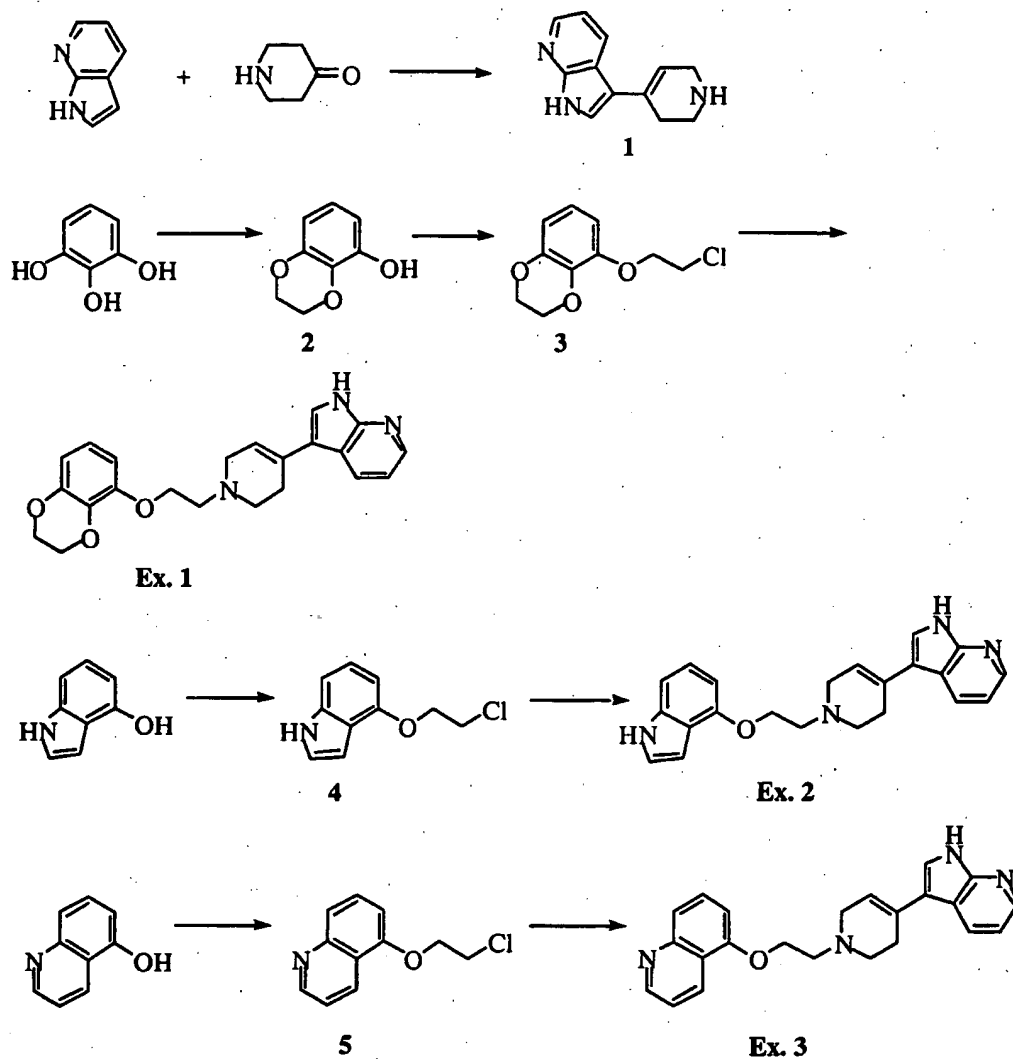
The compounds of Formula I also may be used in the form of a pharmaceutically acceptable acid addition salt having the utility of the free base. Such salts, prepared by methods well known to the art are formed with both inorganic or organic acids, for example: fumaric, maleic, benzoic, ascorbic, pamoic, succinic, 10 bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, oxalic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene-sulfonic, hydrochloric hydrobromic, sulfuric, cyclohexylsulfamic, phosphoric and nitric acids.

15

The compounds of the present invention may be prepared by any suitable method which will be recognized by those skilled in the art. However, the present compounds may be advantageously prepared according to Scheme 1 set forth below.

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Scheme 1



Processes for the preparation of compounds of formula I form a further aspect
5 of the present invention. Specific exemplification of the production of representative
compounds of this invention is provided in the following procedures.

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INTERMEDIATE 1**3-(1,2,3,6-Tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine**

7-azindole (10 g, 85 mmol), 4-piperidone (34 g, 0.22 mol) and potassium hydroxide (16.83 g, 0.3 mol) were heated to reflux in 150 ml methanol overnight.

- 5 The reaction was cooled, filtered and concentrated to give an orange slurry. The slurry was then extracted with methylene chloride and washed with water. The organic layer was dried over anhydrous magnesium, filtered and concentrated to afford 14.2 g (84%) of product as a solid: mp 195-199°C.

INTERMEDIATE 2**5-Hydroxy-(2,3)-dihydrobenzo[1,4]dioxine**

Pyrogallol (5 g, 0.04 mol) was dissolved in 2-butanone (600 ml) to which potassium carbonate (1.82 g, 0.013 mol) was added. The mixture was stirred at reflux while 1,2-dibromoethane (2.48 g, 1.14 ml, 0.013 mol) was slowly added dropwise.

- 15 The reaction was allowed to stir overnight and then cooled to room temperature. The mixture was poured into water (100 ml) and extracted with methylene chloride (200 ml). The organic layer was dried over anhydrous sodium sulfate, filtered, and the solvent was removed under vacuum. Chromatography (5% methanol-methylene chloride) afforded 2.74 g (45%) of product as a clear oil. MS EI *m/e* 152 (*M*⁺)

INTERMEDIATE 3**5-(2-Chloroethoxy)-(2,3)-dihydrobenzo-[1,4]dioxane**

To solution of 5-hydroxybenzodioxane (1.0 g, 6.5 mmol) and 2-chloroethanol (0.79 g, 9.9 mmol), triphenylphosphine (2.6 g, 9.9 mmol) in tetrahydrofuran (50 ml) was slowly added diisopropylazodicarbimide (DIAD) (2.0 g, 9.8 mmol). After 2 hours, another 1.5 eq of triphenylphosphine, DIAD, and 2-chloroethanol was added and the reaction stirred for another 2 hours. The reaction mixture was poured into water (100 ml), and extracted with methylene chloride (100 ml). The organic layer was separated and dried over anhydrous magnesium sulfate, filtered, and the solvent removed under vacuum. Chromatography (20% ethyl acetate-hexanes) afforded 1.7 g (76%) of product as a white solid: mp 70.5-72.5°C.

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Elemental analysis for $C_{10}H_{11}ClO_3$

Cal'd C, 55.96; H, 5.17

Found: C, 55.57; H, 5.20

5

INTERMEDIATE 4**2-(1H-Indol-4-yloxy)ethylchloride**

To a solution of 4-hydroxyindole (4 g, 30 mmol), 2-chloroethanol (4.83 g, 60 mmol), triphenylphosphine (15.7 g, 60 mmol) in anhydrous tetrahydrofuran (40 ml) was slowly added diisopropyl azodicarboxylate (12.1g, 60 mmol). The reaction was
10 allowed to stir for 2.5 hours at room temperature, then poured into methylene chloride (250 ml), washed with water (3 x 100 ml) and dried over anhydrous sodium sulfate, filtered and the solvent was removed under vacuum. Chromatography (20% hexanes-ethyl acetate) to remove triphenylphosphine (20% methylene chloride-hexanes) afforded 2.94 g (50%) of product as a white solid: mp 69.5-72°C.

15

INTERMEDIATE 5**5-(2-Chloroethoxy)-quinoline**

A 100 ml three-neck oven dry flask was cooled under nitrogen. 5-Hydroxy quinoline (2 g, 14 mmol) was added as well as triphenylphosphine (5.42 g, 21 mmol)
20 suspended in 50 ml anhydrous tetrahydrofuran. 2-Chloroethanol (1.3 ml, 21 mmol) was slowly added to above reaction mixture via syringe, followed by adding DEAD (2.98 ml, 21 mmol) via syringe. A second 1.5 eq of 2-chloroethanol, triphenylphosphine and DEAD was added. The reaction mixture was poured into 100 ml water and extracted by methylene chloride. The organic layer was dried over
25 anhydrous sodium sulfate and concentrated. Chromatographed (20% ethyl acetate-hexanes) afforded 2.31 g (82%) of product as a solid: mp 75-78°C.

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EXAMPLE 1

3-{1-[2-(2,3-Dihydro-benzo[1,4]dioxin-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine

A solution of 5-(2-chloroethoxy)-(2,3)-dihydrobenzo [1,4]dioxane (0.5 g, 23 mmol), 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine (0.56 g, 28 mmol) and triethylamine (0.65 ml, 46 mmol) in anhydrous dimethylsulfoxide (20 ml) was allowed to stir for 4 hours at 105°C. The mixture was poured into water (100 ml) and extracted with methylene chloride (3 x 100 ml). The organic layer was washed with water (3 x 150 ml), sodium bicarbonate and dried over anhydrous sodium sulfate, filtered, and the solvent was removed under vacuum. Chromatography (10% methanol-methylene chloride) afforded 0.80 g (92%) of product as a yellow oil.

The oxalate salt was prepared in ethanol: mp 164-167°C

Elemental analysis for $C_{22}H_{23}N_3O_3 \cdot 2C_2H_2O_4 \cdot 0.7H_2O$

Calc'd:	C, 54.77; H, 5.02; N, 7.37
Found:	C, 54.77; H, 4.97; N, 7.23

EXAMPLE 2

3-{1-[2-(1H-Indol-4-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine

A solution of 2-(1H-indol-4-yloxy)ethylchloride (0.5 g, 26 mmol), 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine (0.61 g, 31 mmol) and triethylamine (0.71 ml, 52 mmol) in anhydrous dimethylsulfoxide (20 ml) was allowed to stir for 4 hours at 80°C. The mixture was poured into water and extracted with ethyl acetate (3 x 100 ml). The organic layer was washed with water (3 x 100 ml), sodium bicarbonate and dried over anhydrous sodium sulfate, filtered, and the solvent was removed under vacuum. Chromatography (10% methanol-methylene chloride) afforded 0.95 g (97%) of product as a green oil.

The oxalate salt was prepared in ethanol: mp 106-109°C

Elemental analysis for $C_{22}H_{22}N_4O \cdot 2C_2H_2O_4$

Calc'd:	C, 57.99; H, 4.87; N, 10.40
Found:	C, 57.62; H, 5.03; N, 10.36

EXAMPLE 3

5-{2-[4-(1H-Pyrrolo[2,3-b]pyridin-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethoxy}-quinoline

5 A solution of 5-(2-chloroethoxy)quinoline (0.5 g, 24 mmol), 3-(1,2,3,6-tetrahydro-pyridin-4-yl)-1H-pyrrolo[2,3-b]pyridine (0.58 g, 29 mmol) and triethylamine (0.67 ml, 48 mmol) in anhydrous dimethylsulfoxide (20 ml) was allowed to stir for 4 hours at 80°C. The mixture was poured into water dilute with sodium hydroxide solution and extracted with ethyl acetate (3 x 100 ml). The organic layer was washed
10 with water (3 x 100 ml), sodium bicarbonate and dried over anhydrous sodium sulfate, filtered, and the solvent was removed under vacuum to give a pale yellow solid, which was triturated with ethanol-ethyl ether to afford a pale yellow solid; mp 202-205°C.

The oxalate salt was prepared in ethanol: mp 202-205°C

15 Elemental analysis for $C_{23}H_{22}N_4O \cdot C_2H_2O_4 \cdot 0.5H_2O$

Calc'd: C, 72.80; H, 6.11; N, 14.77

Found: C, 72.71; H, 5.97; N, 15.37

20 The activity of the present compounds is demonstrated by the following standard pharmacological test procedures.

25 The PCR cloning of the human 5-HT_{1A} receptor subtype from a human genomic library has been described previously by Chanda et al., Mol. Pharmacol., 43:516 (1993). A stable Chinese hamster ovary cell line expressing the human 5-HT_{1A} receptor subtype (5-HT_{1A}.CHO cells) was employed throughout this study. Cells were maintained in DMEM supplemented with 10% fetal calf serum, non-essential amino acids and penicillin/ streptomycin.

30 Cells were grown to 95-100% confluency as a monolayer before membranes were harvested for binding studies. Cells were gently scraped from the culture plates, transferred to centrifuge tubes, and washed twice by centrifugation (2000 rpm for 10

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min., 4°C) in buffer (50 mM Tris; pH 7.5). The resulting pellets were aliquoted and maintained at -80°C. On the day of assay, the cells were thawed on ice, and resuspended in buffer. Studies were conducted using [³H]8-OH-DPAT as the radioligand. The binding assay was performed in 96 well microtiter plates in a final
5 total volume of 250 µL of buffer. Comparison experiments were performed by using 7 concentrations of unlabelled drug and a final ligand concentration of 1.5 nM. Non-specific binding was determined in the presence of 10 µM 5HT. Saturation analysis was conducted by using [³H]8-OH-DPAT at concentrations ranging from 0.3-30 nM. Following a 30 minute incubation at room temperature, the reaction was terminated
10 by the addition of ice cold buffer and rapid filtration using a M-96 Brandel Cell Harvester (Gaithersburg, MD) through a GF/B filter presoaked for 30 minutes in 0.5% polyethyleneimine.

A protocol similar to that used by Cheetham et al., Neuropharmacol., 32:737
15 (1993) was used to determine the affinity of compounds for the serotonin transporter. Briefly, frontal cortical membranes prepared from male Sprague-Dawley rats were incubated with ³H-paroxetine (0.1 nM) for 60 min at 25°C. All tubes also contained either vehicle, test compound (one to eight concentrations), or a saturating concentration of fluoxetine (10 µM) to define specific binding. All reactions were
20 terminated by the addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech filtration device to separate bound from free ³H-paroxetine. Bound radioactivity was quantitated using a Wallac 1205 Beta Plate® counter. Nonlinear regression analysis was used to determine IC₅₀ values which were converted to Ki values using the method set forth in Cheng and Prusoff, Biochem. Pharmacol.,
25 22:3099 (1973) ($K_i = IC_{50} / ((Radioligand\ conc.) / (1 + K_D))$).

The [³⁵S]-GTPγS binding assay was similar to that used by Lazareno and Birdsall, Br. J. Pharmacol. 109:1120 (1993). Briefly, 5-HT_{1A} cloned receptor membrane fragments (as used for 5-HT_{1A} receptor binding assays) were stored at
30 -70°C. When needed, membranes were rapidly thawed, centrifuged at 40,000 x g for 10 minutes and resuspended at 4 °C for 10 minutes in assay buffer (25 mM HEPES, 3

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mM MgCl₂, 100 mM NaCl, 1 mM EDTA, 10 uM GDP, 500 mM DTT, pH 8.0). These membranes were then incubated for 30 min at 30 °C with [³⁵S]GTPγS (1 nM) in the presence of vehicle, test compound (one to eight concentrations), or excess 8-OH-DPAT to define maximum agonist response. All reactions were terminated by the
 5 addition of ice cold Tris buffer followed by rapid filtration using a Tom Tech[®] filtration device to separate bound from free [³⁵S]GTPγS. Agonists produced an increase in the amount of [³⁵S]GTPγS bound whereas antagonists produced no increase in binding. Bound radioactivity was counted and analyzed as above.

10 The following assays were performed by incubating the cells with DMEM containing 25 mM HEPES, 5 mM theophylline and 10 μM pargyline for a period of 20 minutes at 37°C. Functional activity was assessed by treating the cells with forskolin (1 uM final concentration) followed immediately by test compound (6
 15 concentrations) for an additional 10 min at 37°C. In separate experiments, 6 concentrations of antagonist were preincubated for 20 min prior to the addition of 10 nM 8-OH-DPAT and forskolin. The reaction was terminated by removal of the media and addition of 0.5 ml ice cold assay buffer. Plates were stored at -20°C prior to assessment of cAMP formation by a cAMP SPA assay (Amersham).

Example No.	5-HT _{1A} (K _i , nM)	ST (K _i , nM,)	GTPγS ED50 (%Emax)	cAMP ED50 (Emax)
1	43.9	18.0	(30%)	
2	10.9	1.46	38.9 (9.0%)	12.4 (0%)
3	71.6	6.89	181 (0%)	90.1 (0%)

20

As demonstrated by the results set forth above, the compounds of the present invention are active towards 5HT_{1A} receptors and generally elevate serotonin levels by
 25 inhibiting 5-HT transport. Accordingly, the present compounds should be useful in treating disorders related to defects in serotonin concentration.

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The compounds of formula I for use in methods of treatment or therapy form further aspects of the present invention.

The compounds of this invention may be administered orally or parenterally, neat or in combination with conventional pharmaceutical carriers. Applicable solid carriers can include one or more substances which may also act as flavoring agents, lubricants, solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents or an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Any of the solid carriers known to those skilled in the art may be used with the compounds of this invention. Particularly suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers may be used in preparing solutions, suspensions, emulsions, syrups and elixirs of the compounds of this invention. The compounds of this invention can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fat. The liquid carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, e.g., cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols (including monohydric alcohols and polyhydric alcohols, e.g., glycols) and their derivatives and oils (e.g., fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in compositions for parenteral administration.

Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or

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subcutaneous injection. Sterile solutions can also be administered intravenously. Compositions for oral administration may be either liquid or solid composition form.

5 Preferably, the pharmaceutical compositions containing the compounds of this invention are in unit dosage form, e.g., tablets or capsules. In such form, the compositions may be sub-divided in unit doses containing appropriate quantities of the present compounds. The unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. Alternatively, the unit dosage form can be, for example, a capsule or tablet
10 itself, or it can be the appropriate number of any such compositions in package form.

The therapeutically effective amount of the compounds of this invention that is administered and the dosage regimen depends on a variety of factors, including the weight, age, sex, and medical condition of the subject, the severity of the disease, the
15 route and frequency of administration, and the specific compound employed, and thus may vary widely. However, it is believed that the pharmaceutical compositions may contain the compounds of this invention in the range of about 0.1 to about 2000 mg, preferably in the range of about 0.5 to about 500 mg and more preferably between about 1 and about 100 mg. Projected daily dosages of active compound are about
20 0.01 to about 100 mg/kg body weight. The daily dose can be conveniently administered two to four times per day.

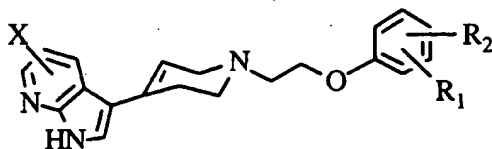
Pharmaceutical compositions comprising the compounds of formula I and a pharmaceutically acceptable carrier form a further aspect of the present invention.
25

The present invention may be embodied in other specific forms without departing from the spirit and essential attributes thereof and accordingly, reference should be made to the appended claims, rather than to the foregoing specification, as indicating the scope of the invention.

- 15 -

WHAT IS CLAIMED IS:

1. A compound of the formula:



- 5 wherein:

R_1 and R_2 form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and

X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;
or pharmaceutically acceptable salts thereof.

10

2. A compound as in claim 1 wherein:

R_1 and R_2 form a heterocyclic ring of 5-6 atoms, and X is hydrogen;
or pharmaceutically acceptable salts thereof.

15

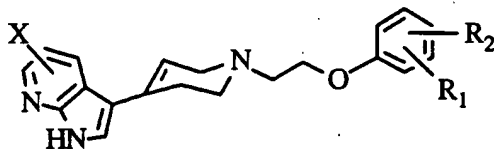
3. The compound of claim 1 which is 3-{1-[2-(2,3-Dihydro-benzo[1,4]-dioxin-5-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine.

4. The compound of claim 1 which is 3-{1-[2-(1H-Indol-4-yloxy)-ethyl]-1,2,3,6-tetrahydro-pyridin-4-yl}-1H-pyrrolo[2,3-b]pyridine.

20

5. The compound of claim 1 which is 5-{2-[4-(1H-Pyrrolo[2,3-b]-pyridine-3-yl)-3,6-dihydro-2H-pyridin-1-yl]-ethoxy}-quinoline.

6. A pharmaceutical composition comprising a compound of the formula:



25

wherein:

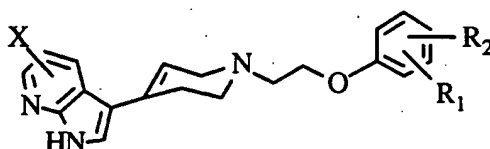
- 16 -

R_1 and R_2 form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and

X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;
or pharmaceutically acceptable salts thereof;

5 and a pharmaceutically acceptable carrier.

7. A compound of the formula



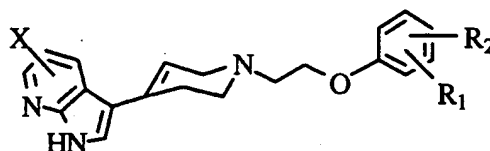
wherein:

10 R_1 and R_2 form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and

X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;
or pharmaceutically acceptable salts thereof; for use in therapy.

15 8. A compound according to claim 7 wherein the use is for treatment of diseases affected by disorders of the serotonin-affected neurological systems.

9. A method for treating depression in a patient in need thereof comprising administering to said patient an antidepressant effective amount of a
20 compound of the formula:



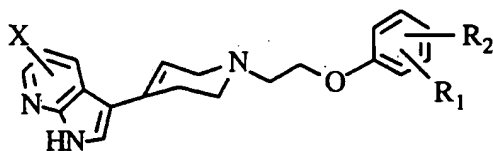
wherein:

R_1 and R_2 form a carbocyclic ring of 5 to 7 carbon atoms, wherein said ring may be
25 saturated or unsaturated and may contain one or more heteroatoms; and

X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;
or pharmaceutically acceptable salts thereof.

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10. Process for the preparation of compounds of formula :



wherein:

5 R_1 and R_2 form a carbocyclic or heterocyclic ring of 5 to 7 atoms, wherein said ring may be saturated or unsaturated; and

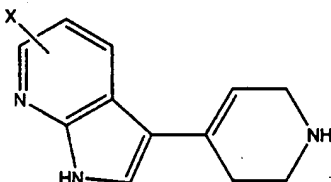
X is independently hydrogen, cyano, carbamoyl, halogen or alkoxy;

or pharmaceutically acceptable salts thereof;

which comprises reacting a compound of formula :

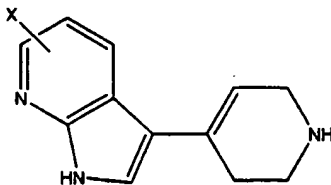


where R_1 and R_2 are as previously defined and Hal is a halogen, with a compound of formula :



15 where X is as previously defined; and optionally forming a pharmaceutically acceptable salt thereof.

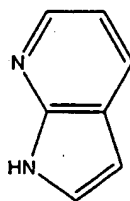
11. Process according to claim 10 in which the compound of formula :



20 where X is as previously defined,

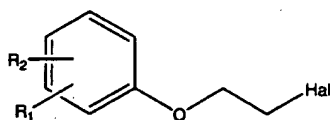
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is prepared by reaction of the compound of formula:

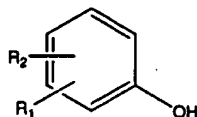


with piperidin-4-one.

5 12. Process according to claim 10 in which the compound of formula :



where R₁, R₂ and Hal are as previously defined is prepared by reacting :



with a corresponding haloalkanol.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/US 00/10628

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/04 A61K31/437 A61P25/24 //(C07D471/04,221:00,
209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EP0-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 722 941 A (LILLY CO ELI) 24 July 1996 (1996-07-24) claim 11; example 148 & US 5 627 196 A (AUDIA ET AL.) 6 May 1997 (1997-05-06) cited in the application	1,8
A	EP 0 714 894 A (LILLY CO ELI) 5 June 1996 (1996-06-05) cited in the application claims 1,7	1,8



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
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- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

G document member of the same patent family

Date of the actual completion of the international search

22 September 2000

Date of mailing of the international search report

04/10/2000

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Int'l. Application No

PCT/US 00/10628

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0722941 A	24-07-1996	US 5576321 A	19-11-1996
		AU 718875 B	20-04-2000
		AU 4651696 A	07-08-1996
		BR 9607077 A	18-11-1997
		CA 2210220 A	25-07-1996
		CZ 9702207 A	18-02-1998
		FI 973024 A	16-07-1997
		HU 9901099 A	28-07-1999
		JP 10512861 T	08-12-1998
		NO 973281 A	08-09-1997
		NZ 301161 A	28-10-1999
		PL 321851 A	22-12-1997
		WO 9622290 A	25-07-1996
		US 5741789 A	21-04-1998
		US 5627196 A	06-05-1997
		US 5614523 A	25-03-1997
		US 5789402 A	04-08-1998
EP 0714894 A	05-06-1996	US 5521197 A	28-05-1996
		CA 2161209 A	02-06-1996
		JP 8225568 A	03-09-1996